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Questionnaire assessments of recent exposure to environmental tobacco smoke in relation to salivary cotinine

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ABSTRACT: The increasing evidence of the ill-health effects of environmental tobacco smoke (ETS) has prompted the search for accurate measures of exposure to ETS. The present study examined whether it was possible to enhance the ability of questionnaire-derived assessments of ETS exposure, to predict salivary cotinine.

Salivary samples were obtained from 258 nonsmoking bank employees, who simultaneously answered questions detailing their exposure to second-hand smoke within the last three days. Exposure models were created, to take into account the number of smokers nearby, length of time in their presence, half-life of cotinine in bodily fluids, level of aversion to cigarette smoke and time of year.

All models, including the consideration of intensity and duration of exposure combined, explained an equal amount of variance of log cotinine levels (approximately 16%).

The weak relationship between questionnaire estimates of ETS exposure and cotinine, found in the present study, suggests that further investigation is needed to improve the assessment of recent ETS exposure.

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The accurate assessment of involuntary exposure to environmental tobacco smoke (ETS) has become important, in the light of growing evidence of its deleterious health effects [1, 2]. Questionnaire information has commonly been used to assess both acute and chronic exposure to ETS, and has been compared to objective measures of exposure, which include biological markers such as salivary cotinine, and air monitoring of ambient levels of nicotine and respirable particulates [3–14].

Previous studies have separately examined duration (hours exposed) and intensity (number of smokers) over varying periods of exposure (1–4 days) as covariables in relation to cotinine levels [10, 11, 14]. In a 10-country collaborative study of the determinants of cotinine levels [15], a comparison was made of questionnaire estimates of duration, intensity and cumulative exposure (cigarettes×time corrected for room volume), at home and at work, by women over the previous 4 days. The estimate of duration better predicted workplace exposure, whereas intensity better reflected home exposure [15]. When considering the cumulative index, each cigarette smoked by the husband in the woman's presence was equivalent to approximately two cigarettes smoked in her workplace. In none of the previous studies was an adjustment made for the half-life of cotinine, estimated to be between 20–40 h, and dependent upon variable metabolic rates between individuals.

The objective of the present study was to determine whether the ability of various questionnaire-derived estimates of ETS exposure to predict salivary cotinine, in both men and women, could be enhanced by considering detailed exposure information from the previous 3 days, and estimating a cumulative index which takes into account the half-life of cotinine.

Patients and materials

The subjects studied were part of a follow-up investigation of the effect of cigarette smoking on ventilatory lung function in young adults [16]. The study population consisted of 251 nonsmokers (no smoking for at least 5 months), who had given a salivary sample suitable for cotinine analysis and completed a questionnaire, out of 391 employees (140 current smokers) from two banks in Montreal and Toronto. Excluded were three subjects who claimed to be nonsmokers but whose cotinine levels were greater than 20 ng·ml^{-1}; these subjects were considered likely to be "deceivers" and were dropped from the analysis, consistent with practice in previous studies [4, 9]. This left 248 nonsmoking subjects for analysis.

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Methods

Questionnaire data

The questionnaire was self-administered at the time salivary cotinine samples were collected, from April 1988 until October 1988. The questionnaire required approximately 15 min to complete, and included questions regarding personal smoking history, exposure to ETS over the period 1981–1988, and of direct concern to the present analysis, questions detailing the previous 3 days of ETS exposure.

For each of the prior 3 days (today, yesterday and the day before yesterday) and each potential place of exposure (work, home, vehicle, social setting and other) subjects were questioned on: 1) type of tobacco smoke exposure (cigarette, pipe and cigar smoke); 2) number of smokers within a 10 ft radius of the subject (intensity), set at a maximum value of five; and 3) duration of exposure in number of hours. Although the type of tobacco smoke was ascertained, they were treated equivalently, due to the rarity of pipe/cigar exposure in this population. Source identity (spouse, friend, *etc.*) for exposure was not ascertained.

Other questions included: 1) the time of day the saliva sample was obtained (morning or afternoon); 2) whether the subject was bothered by ETS (not at all, a little, moderately, or a lot); and 3) the number of hours spent outdoors today, yesterday and the day before yesterday. One subject had a missing value for the aversion variable, which was replaced using the value of three of five subjects with the same age and gender. Laboratory coding and computer entry of questionnaire data was done twice and cross-checked.

Cotinine assay

The salivary sample was analysed at a single hospital laboratory, using a double antibody radioimmunoassay, according to the method described by LANGONE and VAN VUNAKIS [17], and adapted for the determination of cotinine from saliva according to COULTAS *et al.* [9]. The rabbit antiserum was supplied by H. Van Vunakis of Brandeis University. A total of 1.0 ml of undiluted saliva was used for the assay, and the range of measurement from the standard curve was 0.1–2.0 ng·ml^{-1} of cotinine. The interassay coefficients of variation for the 0.6, 0.25 and 2.0 ng·ml^{-1} standards were 4.0, 10.8 and 23.7%, respectively. The laboratory personnel were blinded to the exposure levels of subjects.

Analysis

The dependent variable, salivary cotinine level, was found to be distributed exponentially, consistent with the fact that dose-related serum levels for drugs are often based on first-order kinetics. Therefore, log-transformation was used to normalize cotinine measurement for use in multiple linear regression analyses.

The continuous independent variables were the exposure variables, age and hours outdoors (summed over the previous 3 days). The categorical independent variables were: 1) a weather variable, with three levels according to the months in which subjects were assessed, namely, the coolest two months (April and October), the two months of intermediate temperature (May and September), and the warmest three months (June, July and August); 2) the level of aversion to ETS (four levels described above); and 3) time of sample collection (a.m. or p.m.) [4].

For covariables with ETS exposure (those significantly related to log cotinine at $p<0.05$), mean log cotinine levels for categories were compared using a Bonferroni approach to multiple comparison testing [18], in which each and every pair were statistically compared and adjusted for multiple testing bias. For this analysis, the age variable was broken down into four categories: 20–25, 26–32, 33–38, and 39–44 years old.

Spearman rank correlation coefficients were calculated between the exposure variables and untransformed cotinine. Correlations between the various exposure variables were also examined.

The multiple linear regression analysis was carried out using the SAS general linear models procedure [19]. Different models were based upon different approaches to describing recent ETS exposure using questionnaire responses, and were compared on the basis of the amount of variance of cotinine levels that could be explained by the independent variables selected. The ETS exposure models contrasted included: 1) cumulative exposure (duration (hours exposed to smoke) times intensity of exposure (number of smokers)) *versus* separate duration and intensity covariables; 2) correcting for the approximate half-life of cotinine (1.0 (exposure today) + 0.5 (exposure yesterday) + 0.25 (exposure day before yesterday)) *versus* not correcting for half-life; 3) summing exposure duration and intensity over the previous 3 days *versus* the previous 2 days; and 4) a dichotomous variable of no exposure/any exposure *versus* the continuous expressions of exposure above. The importance of location of exposure was also examined. Covariates from the full model with p-values <0.1 were retained using a backward elimination approach.

Results

A comparison group of four proclaimed smokers had salivary cotinine levels ranging from 95.6–309.1 ng·ml^{-1}, indicating that the radioimmunoassay accurately detected the presence of active smoking. Descriptive characteristics, cotinine levels, and exposures of the 248 nonsmoking men and women are given in table 1.

Spearman rank correlation coefficients between the cumulative exposure variable and cotinine concentration were similar for exposure, corrected and not corrected for the half-life of cotinine (0.26 and 0.28, respectively). This comparability of correlation coefficients for corrected and uncorrected exposure variables was not surprising, given that the correlation between these two exposure variables was 0.99. The correlation between duration and intensity of exposure was also high at 0.79.

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Table 1. – Exposure and descriptive characteristics of subjects

Variable	Men n=125	Women n=123
Mean age yrs	35 (6)	32 (6)
Age groups n subjects		
20–25 yrs	17	17
26–32 yrs	26	43
33–38 yrs	33	44
39+ yrs	49	19
Mean cotinine ng·ml^{-1}	1.1 (1.6)	1.5 (2.3)
Range	0.1–13.3	0.1–14.7
Exposure n subjects		
Yes	75	87
No	50	36
Exposure by location' mean person-hours*		
Work	3.3 (8.7)	6.3 (12.6)
Home	0.2 (1.0)	1.0 (2.1)
Social	1.0 (3.5)	1.5 (5.3)
Vehicle	0.1 (0.5)	0.2 (5.3)
Other	0.1 (0.5)	0.3 (1.4)
Total	4.7 (9.3)	9.3 (14.5)
Mean hours exposed**	2.2 (3.8)	4.4 (5.7)
Mean number of smokers exposed to	2.3 (2.7)	2.9 (3.3)
Aversion to ETS n subjects		
None	5	5
A little	34	37
Moderate	40	42
A lot	46	39
Month category n subjects		
Cool	33	24
Intermediate	63	45
Hot	29	54
Total mean hours spent outdoors	6.6 (4.2)	5.8 (4.6)
Time examined n subjects		
Morning	47	47
Afternoon	78	76

Data are presented as mean and standard deviation in parenthesis. *: cumulative number of smokers × hours exposed, corrected for the half-life of cotinine over 3 days (weights are 1.0, 0.5, 0.25, for exposure on the day of cotinine sampling, the day prior, and 2 days prior, respectively); **: corrected for the half-life of cotinine as above. ETS: environmental tobacco smoke.

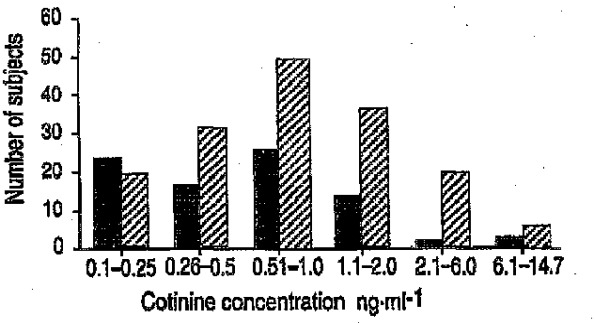

Fig. 1. – Cotinine concentrations in exposed and unexposed subjects. ■: unexposed; ▨: exposed.

Table 2. – Distribution of salivary cotinine levels across categories of variables significantly related to cotinine

Variable	Mean* (SD) log salivary cotinine + 1 Men	Women	Total
Exposure			
Yes**	0.7 (1.0)	0.9 (1.0)	0.8 (1.0)
No	0.2 (1.1)	0.4 (1.1)	0.3 (1.1)
Age Groups			
20–25 yrs	1.1 (1.0)	0.7 (1.1)	0.9 (1.2)
26–32 yrs	0.7 (0.8)	1.1 (1.1)	0.9 (1.0)
33–38 yrs	0.3 (1.2)	0.5 (1.0)	0.4 (1.1)
39+ yrs	0.4 (1.0)	0.8 (1.1)	0.5 (1.0)
Aversion to ETS			
None	1.1 (0.9)	0.6 (0.8)	1.0 (0.9)
A little	0.6 (1.2)	1.1 (1.0)	0.9 (1.1)
Moderate	0.4 (1.0)	0.6 (1.0)	0.5 (1.0)
A lot	0.5 (1.0)	0.6 (1.2)	0.6 (1.1)
Month category			
Cool	0.5 (1.1)	0.4 (0.9)	0.4 (1.0)
Intermediate	0.4 (1.1)	0.7 (1.3)	0.6 (1.2)
Hot	0.7 (1.1)	1.0 (1.0)	0.9 (1.0)

*: transformation used to avoid negative logarithms for cotinine levels <1; **: brackets connecting pairs indicate significant ($p<0.05$) differences between categories, after having accounted for multiple testing bias using Bonferroni comparison tests, for both men and women combined; ETS: environmental tobacco smoke.

It is apparent from Figure 1, that there was considerable overlap in the number of exposed and unexposed subjects within each of six intervals of cotinine concentration. There was, however, on average a greater concentration of cotinine among exposed subjects, evident for both men and women (table 2).

Statistical testing for both genders combined showed differences in mean log cotinine concentrations across categories of the different covariates, and between exposed and non-exposed subjects (table 2). It is evident from the table that trends in the means across categories were not consistent between the two genders. Testing for differences in three day exposure levels between categories of aversion and of temperature failed to reveal differences in log cotinine levels by analysis of variance ($p>0.05$). However, there were significant differences in exposure between age categories for both genders combined. A Bonferroni test showed that the second category (26–32 years old) was significantly different from all of the other categories, with a higher mean level of exposure (11.2 person-hours *versus* 3.0–7.0 person-hours in the other three age categories). Although these differences in exposure may partly explain higher log cotinine levels for ages 26–32 years *versus* the two older categories, the lowest mean person-hours of exposure (3.1) was found in the youngest age category of 20–25 years old, which also had the highest mean cotinine level (1.94 ng·ml^{-1}).

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In the multivariate selection procedure, exposure according to questionnaire, age, level of aversion, and time of year were significantly related to log cotinine values ($p<0.05$), and were included in the final regression models. The variables describing gender, hours outdoors, and the time of day (a.m. or p.m.) were not significantly related to log cotinine in any of the regression models examined (all $p>0.39$). Variables describing the interaction between the exposure variables and each of the covariates were not significant.

All regression models explained approximately 15–16% of the variance of log cotinine levels, including those in which: duration and intensity were treated as joint (cumulative) or separate variables; the previous two or three days of exposure were examined; the half-life of cotinine was or was not corrected for; or a simple dichotomous exposure variable was used. Estimated regression coefficients, their standard errors and significance levels for the final regression models are given in table 3. Note that regression coefficients are not readily interpretable, due to the necessary log transformation of cotinine, and are presented as a means of comparing the different expressions of exposure.

Table 3. – Regression models for the relationship of environmental tobacco smoke exposure to log salivary cotinine levels in nonsmokers*

Model	Exposure variable**	Regression coefficient	Standard error
1	Cumulative	0.015#	0.004
2	Cumulative, corrected for cotinine half-life	0.020##	0.005
3	Duration, corrected for cotinine half-life	0.015NS	0.017
	Intensity, corrected for cotinine half-life	0.063#	0.027
4	Dichotomous exposure (none/any)	0.466##	0.137

*: the dependent variable is log cotinine; other covariates retained in all models included age, time of year, and aversion to environmental tobacco smoke; **: cumulative=duration × intensity for each location and day of exposure; duration=hours exposed, intensity=number of smokers; all exposures are for the previous 3 days; cotinine half-life correction weight are 1.0, 0.5, 0.25, for exposure on the day of cotinine sampling, the day prior, and 2 days prior respectively; #: $p<0.054$; ##: $p<0.001$; NS: not statistically significant, $p>0.05$.

In a model containing cumulative exposure for each separate place of exposure, significant relationships to log cotinine were found for work exposure ($p<0.01$), and in social exposures ($p<0.04$), whereas exposures at home, in vehicles, or at other places were not significant. This was expected since the great majority of reported exposures occurred at work and in social settings (table 1).

Discussion

Self-reported levels of exposure to environmental tobacco smoke were not strongly related to the level of salivary cotinine, with none of the regression models explaining more than 16% of the variability in log cotinine levels. Thus, little difference was found between standard approaches and present attempts to enhance the ability of questionnaire-derived estimates of ETS exposure to predict salivary cotinine, which included: 1) adjustment of previous days' exposure for the half-life of cotinine; and 2) the use of cumulative exposure, the summed product of exposure intensity multiplied by duration. Similar levels of association have been reported by other investigators, who reported that no more than 23% of the variance of cotinine levels could be explained using multivariate approaches [9, 11, 14]. Exceptions to these studies were the findings of JARVIS *et al.* [5], where parental smoking level explained 44% of the variance of salivary cotinine levels in 569 nonsmoking schoolchildren, possibly because exposure was largely limited to a single place, the home. In the present study, most of the exposures (and their strength of relation to cotinine levels) occurred in the office and social settings, where ETS levels were probably determined by the amount of smoking throughout those sections of a building connected by ventilation systems or large open spaces. Therefore, the actual level of tobacco smoking may not have been as apparent to subjects as in the home, thus explaining the considerable overlap in cotinine concentrations in those reporting exposure with those reporting no exposure (fig. 1), a finding consistent with previous reports [8, 20].

It is important to note that the amount of variance explained may differ between study populations, partly because of differences in the range and distribution of estimated exposures, even though the actual relationship between exposure estimates and cotinine remains the same [21]. Part of the low level of concordance between questionnaire-based estimates of ETS exposure and salivary cotinine is due to inaccuracy in the measurement of cotinine. This may have been higher in the present study, due to the high interassay coefficients of variation observed for our cotinine standards. Cotinine concentrations were, however, concordant with a recent review of studies relating salivary cotinine to ETS exposure [22]; most (96%) of the nonsmokers had cotinine concentrations in the typical range of <5.0 ng·ml^{-1}.

In addition to place of exposure, other determinants of exposure to ETS found in the present study were the level of aversion to ETS, age, and the time of year. An increased level of cotinine for the two lower *versus* two higher levels of aversion was only apparent in men. Higher levels of cotinine were found in the two younger *versus* the two older age categories, similar to findings reported by CUMMINGS *et al.* [14]; however, it was not possible to attribute this finding to differences in exposure, and results differed by gender. The finding that warmer months were associated with higher cotinine levels than cooler months is likely to be spurious, since it is contrary to the findings of previous reports [11, 14], it could not be explained by differences in exposure, it was limited to women, and subjects studied during different months differed as to the place of work (one of two banks).

The modelling approaches in the present study should be re-examined in different settings, to confirm or reject the lack of improvement in the ability of a detailed

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questionnaire-derived model to predict cotinine. Our findings do suggest, however, that the cumulative exposure estimate was related more significantly to cotinine ($p<0.001$) than were intensity ($p<0.02$) or duration ($p<0.38$) as exposure covariables. The lack of an independent effect of duration is in contrast to the results of COULTAS *et al.* [11], who found that hours of exposure was the only significant predictor of salivary cotinine.

The present study did not completely account for cumulative exposure, since only the place and each day of exposure could contribute to estimates, not every hour of exposure. A preferable set of questions, as suggested by O'NEILL *et al.* [23], would provide more precise exposure profiles by listing on the questionnaire several lines for each day and each place of potential exposure, with responses to be filled in as: number of smokers for number of hours. Investigators designing questionnaires for studies of acute responses to ETS exposure may gain precision from such an approach.

In the present study, the weak relationship between questionnaire responses and salivary cotinine pertains to recent, not chronic ETS exposures, and thus to studies of the acute health effects of recent exposure. Cotinine as a biological marker of ETS exposure is useful in such studies, given its relatively long half-life and its objective nature, although contradictory findings in the literature argue against considering salivary cotinine to be a gold standard of exposure estimation [24, 25]. Also, from the present study and other similar investigations, it appears that questionnaire assessments of recent ETS exposure are inaccurate, given the low levels of concordance with cotinine despite the use of conceptually better exposure estimates. Further efforts appear necessary to improve the assessment of recent ETS exposure, with investigations aimed at verifying the success of such efforts.

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